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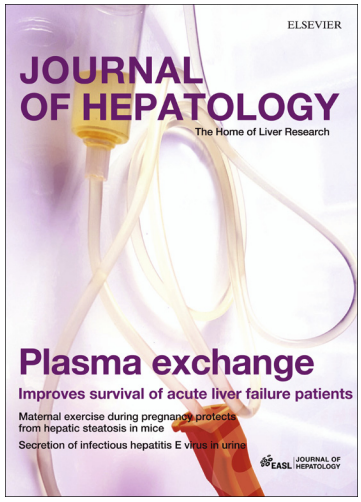

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Cohort study of the impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis

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Abbreviations

DAA – direct acting antiviral

HCV – hepatitis C virus

EAP - Expanded access programme

SVR – sustained virological response

MELD – model for end stage liver disease

ALT – alanine aminotransferase

RNA - ribonucleic acid

HIV - human immunodeficiency virus

SAE – serious adverse event

BMI – body mass index

LLQ - lower limit of quantification

ROC – receiver operating characteristic

AUC – area under the curve

Sof – sofosbuvir

DCV – daclatasvir

LDV – ledipasvir

RBV – ribavirin

OR – odds ratio

CI – confidence interval

Hb – haemoglobin

OLT – orthoptic liver transplant

Key words

Hepatitis C virus, sofosbuvir, ledipasvir, daclatasvir, MELD score, decompensated cirrhosis

Conflict of interest

Professor Foster has received speaker and consultancy fees from AbbVie, Achillion, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Idenix, Janssen, Merck, Novartis, Roche, Springbank

Professor Irving has received speaker and consultancy fees from Roche Products, Janssen Cilag and Novartis, educational grants from Boehringer Ingelheim, MSD and Gilead Sciences, and research grant support from GlaxoSmithKline, Pfizer, Gilead Sciences and Janssen Cilag

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Authors' contributions

The study was designed and led by GRF, WI and KA. MC, BH, SV managed patients in the study, collated the data and assisted in the analysis. AW performed the data and statistical analysis. WI and JM supervised sample collection, data management and assisted with study design and implementation. DJM, AB, WG and DCM led the recruitment and data collection. All authors participated in data analysis and participated in the preparation of the manuscript.

Abstract

Background and Aims

All oral direct-acting antivirals (DAAs) effectively treat chronic hepatitis C virus (HCV) infection, but the benefits in advanced liver disease are unclear. We compared outcomes in treated and untreated patients with decompensated cirrhosis.

Methods

Patients with HCV and decompensated cirrhosis or at risk of irreversible disease were treated in an Expanded Access Programme (EAP) in 2014. Treatment, by clinician choice, was with sofosbuvir, ledipasvir or daclatasvir, with or without ribavirin. For functional outcome comparison, untreated patients with HCV and decompensated cirrhosis who were registered on a database 6 months before treatment was available were retrospectively studied. Primary endpoint was sustained virological response 12 weeks post antiviral treatment (treated cohort) and the secondary endpoint (both cohorts) was adverse outcomes (worsening in MELD score or serious adverse event) within 6 months.

Results

467 patients received treatment (409 decompensated cirrhosis). Viral clearance was achieved in 381 patients (81.6%) – 209 from 231 (90.5%) with genotype 1 and 132 from 192 (68.8%) with genotype 3. MELD scores improved in treated patients (mean change -0.85) but worsened in untreated patients (mean + 0.75) ($p<0.0001$). Patients with initial

serum albumin <35 g/l, aged >65 or with low (<135 mmol/L) baseline serum sodium concentrations were least likely to benefit from therapy.

Conclusions

All oral DAAs effectively cured HCV in patients with advanced liver disease. Viral clearance was associated with improvement in liver function within 6 months compared to untreated patients. The longer term impact of HCV treatment in patients with decompensated cirrhosis remains to be determined.

Introduction

All oral direct-acting antiviral (DAA) drugs for patients with chronic hepatitis C virus (HCV) infection have transformed treatment options. High response rates are observed in patients with compensated cirrhosis in clinical trials [1-4] and in real-life observational studies [5]. Even in patients with decompensated cirrhosis, for whom pegylated interferon is contraindicated and who otherwise have a poor prognosis, HCV can now be cured safely and effectively [6]. Experience of different DAA combinations in the real world is growing within a number of compassionate use programs [5,7]. However, virological response with all oral DAAs in decompensated cirrhosis, particularly in HCV genotype 3, is lower than in patients with less advanced liver disease [8,9]. Remaining uncertainties in treating such patients include the optimal duration of therapy, whether or not the regimen should include ribavirin, and what, if any, clinical benefits accrue to patients with such advanced liver disease following clearance of virus.

Viral eradication in patients with chronic HCV infection has been shown to result in improvements in medium and long term outcomes – assessed both by patient reported quality of life measurements and mortality/morbidity [10-12]. However in patients with advanced, decompensated cirrhosis it is uncertain whether treatment and viral clearance is beneficial, and if meaningful functional hepatic recovery is possible. Clearly if treatment were able to reverse liver dysfunction and perhaps avoid the need for transplantation then therapy should be recommended. However therapy, although generally safe, might be associated with adverse events, particularly in unstable patients with advanced cirrhosis [13] and may delay access to transplantation. It is conceivable that patients with decompensated cirrhosis may eliminate virus, stabilise

their disease and not progress to a stage where transplantation is indicated. However, they may not recover to any meaningful extent and, post therapy, may be left without access to transplantation but with a poor quality of life (so called 'MELD purgatory'). In the SOLAR study of patients with advanced liver disease infected with HCV genotypes 1 and 4, viral eradication was rapidly associated with an improvement in severity of liver disease scores (MELD scores) [6] but no comparator group was included, and it is unclear whether benefits were related to viral clearance or to improved management of the patients in a clinical trial setting in specialist centres [1-3].

Here we report on the outcomes of the NHS England Expanded Access Programme (EAP), which treated patients with severe liver disease of all viral genotypes, who were "at significant risk of death or irreversible damage within 12 months due to hepatic or extra-hepatic manifestations". Sofosbuvir combined with the NS5A inhibitors ledipasvir or daclatasvir, with or without ribavirin, was used for a fixed duration of 12 weeks and patients were enrolled in the UK hepatitis C registry – HCV Research UK. To address the question of whether antiviral therapy is beneficial in unselected patients with decompensated cirrhosis infected with all HCV genotypes, we examined the functional outcomes of patients with equivalent disease stage, who enrolled into the same registry for at least 6 months prior to the start of EAP, and hence were not able to receive HCV treatment for at least 6 months of follow-up. We show that HCV treatment improves outcomes and we present a model to predict those patients who are likely to derive most benefit from therapy.

Patients and Methods

Study design and patients

For treated patients this was a prospective, observational cohort study. Patients enrolled in the HCV Research UK registry who received antiviral therapy as part of the EAP between 1 April 2014 and 11 November 2014 were studied. Eligible patients were those at significant risk of death or irreversible damage from HCV infection within 12 months, irrespective of genotype. Criteria for inclusion were decompensated cirrhosis - ascites, variceal bleed or encephalopathy (past or current), Child Pugh score ≥7, or non-hepatic manifestation of HCV likely to lead to irreversible damage in 12 months and intolerant to, or failed, pegylated interferon and ribavirin therapy, or exceptional circumstances (determined by a review panel). Treatment was chosen by the prescribing clinician and involved either ledipasvir/sofosbuvir or sofosbuvir/daclatasvir, both with or without ribavirin for a total of 12 weeks. Prescribing was restricted to 20 English centres selected by NHS England in a competitive tender process, and comprised experienced HCV treatment centres. A criterion for participation in the bid was participation in HCV Research UK ensuring that data could be collected from all treatment sites. All patients receiving therapy were asked to consent to contribute anonymised data to the national registry, and those who agreed were included.

For the comparator population (untreated) we used a retrospective, observational study design. Patients were selected from the HCV Research UK database. Inclusion criteria were decompensated cirrhosis (defined by the criteria above) who were enrolled before 1 October 2013 (i.e. enrolled in the database 6 months before the EAP was initiated),

and patients subsequently included in the EAP who had been enrolled in the database 6 months prior to the initiation of therapy.

The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Ethics approval for HCV Research UK was given by NRES Committee East Midlands - Derby 1 (Research Ethics Committee reference 11/EM/0314) and informed consent was obtained from each patient included in the study. Patients who declined to enrol in HCV Research UK were given antiviral therapy but data was not collected.

Treatment

All patients received a maximum of 12 weeks therapy. Sofosbuvir (400mg per day) was purchased from Gilead and clinicians chose to combine it with either ledipasvir (90mg per day), provided by Gilead as a single tablet co-formulation with sofosbuvir, or with daclatasvir (60mg per day, with dose adjustment to 30mg or 90mg per day as recommended in patients with relevant potential drug-drug interactions) which was provided by Bristol-Myers Squibb. Inclusion and dosage of ribavirin was discretionary according to the treating clinician.

Monitoring

Patients receiving therapy were reviewed at treatment weeks 2, 4, 8 and 12, and post treatment weeks 4 and 12. Clinical events were recorded on a standardised form and local accredited laboratories measured serum creatinine, bilirubin, albumin, alanine aminotransferase (ALT), sodium, HCV RNA level, full blood count and clotting profile, which were recorded for each study visit. Missing or late values during therapy were

ignored, and missing values from the initiation visit or week 12 post treatment visit were derived from the nearest adjacent test value taken before or after therapy respectively. MELD scores were calculated centrally using site-derived laboratory parameters.

Serious adverse events, specifically any hospital admissions, decompensation events, liver transplantation, other complications of end-stage liver disease (including hepatocellular carcinoma) and death were recorded.

Baseline demographic data (age, gender, ethnicity, body mass index (BMI), alcohol use, previous treatment history, decompensation events and HIV serostatus) and HCV genotype were taken from the original registration form recorded on the HCV Research UK database.

Outcome measures

The primary outcome was sustained virological response 12 weeks post treatment (SVR12) defined as undetectable HCV RNA measured at an accredited local laboratory with a lower limit of quantification (LLQ) of <30 IU/ml. Secondary outcomes included change in MELD score, and adverse clinical events during the study period. Overall adverse clinical outcome was defined as the composite of a MELD score increase by 2 points or more, and/or occurrence of any serious adverse event. For patients who were enrolled in the comparator cohort, the responsible clinician reported the same events in a pre-defined form.

All analyses were by intent to treat - patients who received a liver transplant during therapy who did not complete 12 weeks' therapy were regarded as having achieved

SVR12 if they had undetectable viral load at 24 weeks from start of treatment; subjects who were lost to follow up were regarded as treatment failures.

Data analysis

For the primary analysis (SVR12) comparisons were made using Chi-square. Predictors of relapse were also assessed using a logistic regression analysis in which only patients with a known virological outcome were included. Initially we used a univariable model, then all factors were included in a multivariable model, except for those that were likely to be highly collinear (i.e. Child Pugh score which was removed in favour of MELD score).

For all functional outcomes analysis, patients were excluded if they were transplanted before treatment or if treatment was for an extra-hepatic indication. The proportion of patients with adverse clinical outcomes was determined and subsequently stratified by various baseline characteristics. The significance of any difference between the treated and comparison group were determined using Chi-squared tests. For calculations of MELD changes, we excluded patients who received a liver transplant during the study period, in order to evaluate MELD progression in patients with decompensated cirrhosis over 6 months with and without treatment. Similarly patients who died before study end, who did not have a MELD score at 6 months, were excluded from this analysis. The EAP and comparison cohort were then plotted in separate waterfall plots. We performed a sensitivity analysis excluding current alcohol users (of any number of units, within one month of study start date) to assess the potential impact of differences in alcohol use between the treated and untreated cohorts. Predictors of clinical benefit at baseline

(defined as a lack of serious adverse event and no increase in MELD score) was analysed using logistic regression. Predictors were assessed if they were determined *a priori* to plausibly influence outcome, including age, gender, body mass index, alcohol use (never, past or current), baseline MELD score, creatinine, albumin, platelets and sodium. The interactions between albumin and age, and baseline sodium, were also explored *a priori*. Internal validation was carried out using bootstrapping (50 iterations), with a 70% derivation sample. This generated a receiver-operating characteristic (ROC) curve, from which the area under the curve (AUC) was calculated. Model simplicity was prioritised, with additional factors only being accepted into the model if the AUC increased by more than 0.02.

Data handling and statistical analysis were performed using STATA 13.1 with additional analysis performed using Orange 2.7.8.

Results

Participants

Treatment cohort

A total of 480 patients received therapy as part of the EAP between the start of the programme (1 April 2014) to 11 November 2014; 467 patients consented to provide data to the HCV Research UK database (Figure 1). At treatment initiation 409 (88%) patients had decompensated cirrhosis and/or Child Pugh score ≥7; 44 (9%) had undergone liver transplantation with aggressive HCV recurrence without decompensation. The remaining 14 (3%) patients were treated for extra-hepatic indications. Table 1 and Supplementary Table 1 show the baseline characteristics of the treated cohort. A higher proportion of genotype 3 patients received daclatasvir compared to genotype 1 (125/192 (65%) vs. 46/231(20%)), and clinicians chose to add ribavirin to the regimen for most (427/467 (91%)) patients (Table 2).

Comparator cohort

From the HCV Research UK database we identified 261 patients with decompensated HCV cirrhosis who fulfilled the criteria for inclusion in the study (Figure 1). Study start dates for these patients were between 5 October 2012 to 11 September 2014 and 177 (68%) patients subsequently received antiviral therapy on the EAP after its initiation on 1 April 2014. The treated and untreated cohorts had similar baseline characteristics and liver disease severity scores (Table 1). Amongst the comparator patients who did not

receive EAP therapy, there was a higher proportion of active alcohol users (23%) compared to those who subsequently received treatment (12.6%).

Virological outcomes

Sustained virological response (SVR12) was 381/467 (81.6%) overall for this population of patients with severe HCV disease at risk of death or irreversible harm within 12 months (Table 2 and Figure 2). 51 patients (10.9%) responded but relapsed, 2 (0.43%) were non-responders, 17 (3.6%) died and 16 (3.4%) were lost to follow-up (Supplementary Table 2). Response was markedly influenced by genotype – SVR12 was achieved in 209 of 231 (90.5%) patients infected with genotype 1 compared to 132 of 192 (68.8%) patients with genotype 3 ($p<0.0001$). There was no statistically significant difference in response between ledipasvir- or daclatasvir-containing regimens in either genotype groups. SVR12 with ledipasvir/sofosbuvir and sofosbuvir plus daclatasvir, with or without ribavirin, was 91.9% (170/185) and 84.8% (39/46) respectively ($p = 0.14$) for genotype 1 infected patients, and 61.2% (41/67) and 72.8% (91/125) ($p=0.098$) for genotype 3 infected patients. The addition of ribavirin numerically increased response (352/427 (82.4%) versus 29/40 (72.5%), $p=0.11$).

Of note, 19 patients had virus detectable at levels below the lower limit of quantification (LLQ, 30 IU/ml) after 12 weeks of therapy, and a further 4 patients “blipped” detectable virus below LLQ at 16 weeks (i.e. 4 weeks after end of therapy). 22 of these 23 patients subsequently achieved SVR12, including all 4 of the latter group.

We examined baseline factors that might predict virological failure (Supplementary Table 3). In this analysis we included only patients with documented virological failure and by multivariable analysis, genotype 3 (OR=10.3, 95% CI 4.4-24.6), BMI >30 kg/m^2 (OR=2.9, CI 1.1-8.2) and detectable virus at treatment week 2 (OR=2.6, CI 1.1-6.3) were significantly associated with virological failure. The impact of detectable week 2 viral load was greater in patients with genotype 3 than genotype 1. For patients with genotype 3 HCV, virological failure in those with and without detectable virus at treatment week 2 was 32/105 (30.5%) and 7/70 (10.0%) respectively (p=0.00143). For those with genotype 1 HCV, virological failure in patients with detectable virus at week 2 was 8/141 (5.7%) compared to 4/79 (5.1%) in patients with undetectable virus (p=0.84). Therapy without ribavirin (OR=9.0, CI 2.5-31.0) and therapy with ledipasvir compared to daclatasvir (OR = 2.7 CI 1.2-6.3) were also significantly associated with virological failure, although this latter finding was likely driven by the differential response in patients with genotype 3 infection, which showed numerical advantage with daclatasvir over ledipasvir.

Treatment safety

Treatment with sofosbuvir and an NS5A inhibitor in this patient group with advanced liver disease and/or complex extrahepatic complications was well tolerated. Serious adverse events comprised mainly complications of end-stage liver disease (Supplementary Table 4). Twenty six patients (5.6%) discontinued treatment prematurely, including 7 who died on treatment. Most patients (306/427) treated with ribavirin received the recommended dose of 1.2g per day for patients weighing > 75 kg and 1 g per day for others, 18.7% of patients receiving ribavirin required dose

reductions and 9.6% discontinued ribavirin. The median ribavirin dose was 1g per day. There were only 8 patients with baseline haemoglobin (Hb) below 80 g/L, all but one had ribavirin omitted from their regimen. Grade 3/4 anaemia (Hb ≤ 80 g/L) occurred in 23 (5.4%) patients receiving ribavirin. Development of acute kidney injury on treatment (defined as creatinine increase of 1.5-fold or higher at treatment week 12 compared to baseline) was infrequent, occurring in 13/467 (2.8%) patients.

Functional outcomes

We examined only patients with decompensated cirrhosis and/or Child Pugh score B or worse in this analysis (n=409). Liver function over a 6 month period (3 months on therapy and 3 months post therapy) was compared to the untreated cohort. Figure 3 and Supplementary Table 5 show MELD score changes and development of adverse clinical outcomes within the two cohorts. Treated patients had a mean negative change in MELD (-0.85, SD 2.54) representing improvement in liver function, whereas untreated patients had a mean positive change (0.75, SD 3.54) representing worsening in liver function ($p<0.0001$). Significantly fewer treated patients developed a profound worsening in MELD (increase of 2 points or more) over 6 months compared to untreated patients (23.0% vs 37.9%, $p=0.05$). The proportion of patients with at least one decompensating event during the study period was reduced in the treated compared to untreated cohort, apart from the subgroup with baseline MELD score >14. Rates of new decompensation (i.e. development of decompensating event(s) in a patient with recompensated disease at baseline) were significantly lower in the treated cohort (3.7% versus 10.0%, $p = 0.0009$) compared to the untreated cohort. There were no significant differences between treated and untreated patients in the incidence of hepatocellular

carcinoma, sepsis or death. Overall adverse clinical outcomes (composite of MELD worsening by 2 or more and/or any serious adverse event) were 52.3% in the treated group and 63.6% in the untreated group (p=0.004).

For treated patients, SVR12 status did not predict MELD score change. However, a smaller proportion of patients who achieve SVR12 had an increase in MELD score ≥2 compared to those who did not achieve SVR12 (11.9% versus 68.8%). Adverse outcomes for patients with and without SVR12 were 45.0% and 82.5% (Supplementary Table 5).

To determine whether or not alcohol consumption (which differed in the treated and untreated populations) impacted outcomes, we analysed functional response after excluding patients who were active alcohol users (of any amount) at baseline (Supplementary table 6). Among patients who were past or never users of alcohol, greater extents of improvement were observe in those who received treatment than untreated patients (mean change in MELD score -0.86 versus 0.68; composite adverse outcome in 52.0% versus 61.7%).

Overall adverse outcomes were more frequent in patients with high baseline MELD and low albumin (≤35g/L) for both treated and untreated groups (Supplementary Table 5). For patients with decompensated cirrhosis, we assessed whether baseline characteristics might be useful in predicting functional benefit gained from therapy. We defined functional benefit as no MELD score worsening and no development of serious adverse events following treatment. Patients older than 65 years with reduced synthetic function (serum albumin ≤35 g/L) had the lowest odds of deriving functional benefit with

antiviral treatment (Table 3). However the model was not robust with a ROC area under the curve of 0.5484 (Supplementary Figure 1). Alternatively, using baseline sodium level with a cut-off at 135 mmol/L increases the AUC to 0.5797 (Supplementary Figure 2). We did not study the interaction of all three factors due to insufficient number of patients within the subgroups.

Discussion

The efficacy of all-oral antiviral regimens in the management of patients with compensated liver disease due to chronic HCV infection is now established [1-4] and data on patients with decompensated cirrhosis are emerging [5-7,14]. In this study we examined a fixed, 12 week, duration course of antiviral therapy in a large heterogeneous group of patients with decompensated cirrhosis or life-threatening complications of HCV infection, and we compared outcomes to an untreated cohort with equivalent disease and duration of follow up.

The EAP study was robustly conducted with prospective, standardised monitoring and reporting through a central database - HCV Research UK. The majority of treated patients were included in this report (only 13 patients declined to participate) thus reflecting a true 'real-life' cohort, and a large number of patients infected with genotype 3 were included for the first time. The inclusion criteria for EAP treatment was patients with significant risk of death or irreversible harm within 12 months, mostly with decompensated cirrhosis. Markers of liver disease severity such as MELD score and platelet count were similar to other studies of HCV treatment in decompensated patients (SOLAR-1, ASTRAL-4) [6, 14]. Within the decompensated subgroup, 17% patients were Child Pugh class A at baseline, but had past decompensation events, and therefore remained at significant risk from severe liver disease. Importantly for the comparator group we selected patients who enrolled in the cohort before therapy was available, thereby reducing the inherent bias in selecting treated patients with prior follow up.

We noted excellent virological response rates in patients infected with genotype 1 HCV regardless of choice of NS5A inhibitor, but response was statistically significantly lower

in patients with genotype 3 HCV. In this non-randomised study SVR was numerically higher in patients with genotype 3 infection who received daclatasvir compared to ledipasvir, although the clinical relevance of this observation is not addressed in this study.

Aside from treatment regimen, we found the presence of detectable HCV RNA at treatment week 2 was an independent predictor of virological failure, and was a stronger predictor than previous treatment history or markers of severe liver disease such as high MELD score or thrombocytopenia. This finding is novel to other analyses of treatment response evaluating only genotype 1 patients with less advanced cirrhosis [15] and was most marked in patients with genotype 3 infection. On-treatment viral response may help to guide the need for extension to 24 weeks of therapy in patients with a lower likelihood of a clinical response, specifically patients with genotype 3 infection.

The beneficial role of ribavirin in treating patients with decompensated cirrhosis is suggested by improved virological response rates in ribavirin-containing regimens (whether combined with ledipasvir or daclatasvir), particularly for patients infected with genotype 3. However the total number of patients treated without ribavirin was small and although no clear adverse events were associated with ribavirin, robust conclusions cannot be drawn. While the clinical trial of ledipasvir/sofosbuvir in patients with decompensated cirrhosis did not include a ribavirin-free arm (SOLAR-1), in ASTRAL-4 which treated 267 patients infected with genotypes 1 to 6 and decompensated cirrhosis with 12 weeks of sofosbuvir and velpatasvir, with or without ribavirin, and 24 weeks of sofosbuvir and velpatasvir alone, ribavirin showed a clear advantage. The study was not

powered to detect significance between the three treatment groups, but the addition of ribavirin increased SVR, and to a greater extent than the 24 week duration, particularly in genotype 3 infected patients. [14]

Not unexpectedly from this population with advanced disease, serious adverse events were common, comprising mainly events related to end-stage liver disease. However, treatment was well tolerated with few premature discontinuations.

To assess the impact of antiviral treatment in decompensated cirrhosis, we selected a comparator cohort from patients registered in the national database HCV Research UK who had decompensation, and retrospectively monitored the change in MELD scores and development of serious adverse events over a 6 month period. Patients from both treatment and comparator cohorts were selected from the same network of experienced HCV treatment centres, thus reducing the impact of 'improved care' in patients receiving antiviral therapy. Amongst treated patients a greater proportion showed an improvement in MELD scores, and for patients who had worsened MELD the degree of worsening was less compared to untreated patients, suggesting benefits of therapy within 6 months. This was observed even for patients who failed treatment (mean MELD change -0.63), who nevertheless experienced several months of non-viraemia prior to relapse. We studied a composite endpoint of MELD worsening and development of any serious adverse events, rather than limiting to liver-related events, which we felt was the most clinically useful endpoint. Treated patients had significantly fewer adverse outcomes, with MELD score change and number of decompensation events being the main contribution to the outcome difference, while liver cancers, transplants and deaths were not significantly different over this 6 month period. Treated patients who achieved

SVR12 had considerably better functional outcomes than those who were treated but failed to achieve SVR12 (adverse outcomes 45.0% and 82.5% respectively).

This study was not a randomised controlled trial of treatment versus no treatment, which would be unethical. Wherever possible we attempted to reduce biases in the untreated comparison population. Patients were selected from the HCV Research UK database prior to treatment becoming available. Whilst this population may contain patients who were not treated subsequently because they died or deteriorated to a stage where treatment could not be considered, it also contains patients who survived and were fit enough to receive treatment through the EAP. By using the entire available 'pre-EAP' population, we reduced the possibility of selecting only patients who were fit enough to receive antiviral therapy and we minimised bias. It is possible that differences in severity of liver disease remained between the treated and untreated groups, but these were not evident at baseline measurements, with the exception of alcohol consumption which was greater in the comparator cohort. As this may have contributed to the increased adverse outcomes in the untreated population, we performed a post-hoc analysis excluding active alcohol users in both groups, and found a similar improvement in MELD in treated patients, worsening in MELD and increased adverse outcomes for untreated patients. Monitoring of the untreated group was retrospective but was prospective for the treated group, which might bias the study towards a relative under-reporting of events within the comparator cohort.

Finally we attempted to develop a prediction model for functional outcomes after antiviral treatment to identify patients most likely to benefit from therapy. Regression analysis of baseline characteristics and association with MELD change yielded baseline

MELD score as the only significant independent factor. We combined age and serum albumin data and found older patients with poor synthetic function to have a substantially lower chance of benefit compared to younger patients with preserved synthetic function (39.3% vs 60.5%, p=0.050). Given the importance of sodium as a variable in predicting mortality risk in addition to MELD score, we analysed the odds ratio of benefit at a cut-off of 135 mmol/L and showed that patients with normal range sodium levels to have higher chance of treatment benefit than patients with hyponatraemia (51.1% vs 39.1%, p=0.023). This model did not show sufficient discrimination to allow it to be used to recommend that treatment should be withheld nor is it robust enough to recommend that a patient proceed with liver transplantation, if appropriate. However, given that interferon-free therapy has opened up treatment options for vulnerable patients, the risk estimates provided within the modelling may help clinicians when they discuss the risks and benefits of all oral treatment with patients. Reports of decompensation on DAA therapy for patients with advanced cirrhosis [13] reiterates the importance of such discussions and the need for a careful evaluation of the different options on a case by case basis.

In summary, this is a large real-life study of all-oral HCV therapy in patients with advanced HCV disease with a significant risk of death or irreversible damage within 12 months. Overall virological response was high and we found early improvement in liver parameters and in clinical outcomes after antiviral treatment, compared to untreated patients. The longer term benefits of therapy in patients with decompensated disease remain to be ascertained.

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Figures

Figure 1. Derivation of treated and comparator patient cohorts.

Figure 2. Sustained virological response rates at 12 weeks post therapy for patients with decompensated cirrhosis. Error bars represent 95% confidence intervals.

Figure 3. Changes in MELD score over 6 months in treated (upper panel) and untreated (lower panel) patients who survived for the duration of follow up.

Patients who did not achieve an SVR are highlighted in pale grey and patients who died (n=32) and thereby could not achieve a second MELD assessment were excluded

Characteristic		Treated Cohort All (%)	Decompensated	Baseline liver transplant	Extra hepatic indication	Untreated Cohort Total (%)
Total patients		467	409	44	14	261
Age (years)	median	54 (28-80)	54 (28-79)	62 (32-75)	58 (35-80)	54 (33-77)
Gender	Male	339 (72.6%)	297	35	7	214 (82.0%)
Ethnicity	Caucasian	347 (74.3%)	302	34	11	230 (88.1%)
Prior therapy	Yes	284 (60.8%)	244	33	7	162 (62.1%)
	with DAA*	17 (3.6%)	14	3	0	
HIV infected	Yes	23 (4.9%)	20	2	1	6 (2.3%)
Virology						
Genotype	1	231 (49.3%)	200	26	5	129 (49.4%)
	3	192 (41.1%)	172	14	6	90 (34.5%)
	Other	44 (9.4%)	37	4	3	42 (16.1%)
Viral load (iu/mL)	median	280511	255279.5	1006189	2091786	208688
	range	(17-17835823)	(17-13613875)	(71.5-17835823)	(2189-7838385)	(80-23100000)
Liver/renal status						
Bilirubin (µmol/L)	median, range	27 (4-433)	28 (4-433)	18 (5-82)	14 (5-30)	26 (3-335)
Albumin (g/L)		31 (17-55)	31 (17-55)	35 (23-48)	36 (29-46)	32 (10-46)
MELD		11 (6-32)	12 (7-32)	11 (6-25)	10 (6-15)	11 (6-32)
Creatinine (µmol/L)		69 (32-477)	66 (32-477)	98 (60-286)	75 (48-206)	68 (25-340)
ALT (U/L)		53 (8-594)	54 (8-345)	44 (17-594)	48 (24-156)	
Platelets (x10^9/L)		74 (3-321)	72 (20-277)	116 (3-321)	114 (17-233)	70 (3-358)
Child Pugh Score	B n (%)	319 (68.3)	297 (72.6)	21 (47.7)	0 (0.0)	
	C	43 (9.2)	41 (10.0)	2 (45.5)	0 (0.0)	
Ascites	Present	197 (42.2)	183 (44.7)	14 (31.8)	0 (0.0)	
Alcohol use	Current	59 (12.6%)	53	3	3	60 (23.0%)
	Never	95 (20.3%)	80	10	5	53 (20.3%)
	Past	281 (60.2%)	246	31	4	135 (51.7%)
	Unknown	32 (6.9%)	30	0	2	13 (5.0%)
Treatment	Sof/DCV	15 (3.2%)	12	1	2	
	Sof/DCV/RBV	172 (36.8%)	150	17	5	
	Sof/LDV	25 (5.4%)	18	7	0	
	Sof/LDV/RBV	255 (54.6%)	229	19	7	

* DAA = with protease inhibitors boceprevir/telaprevir

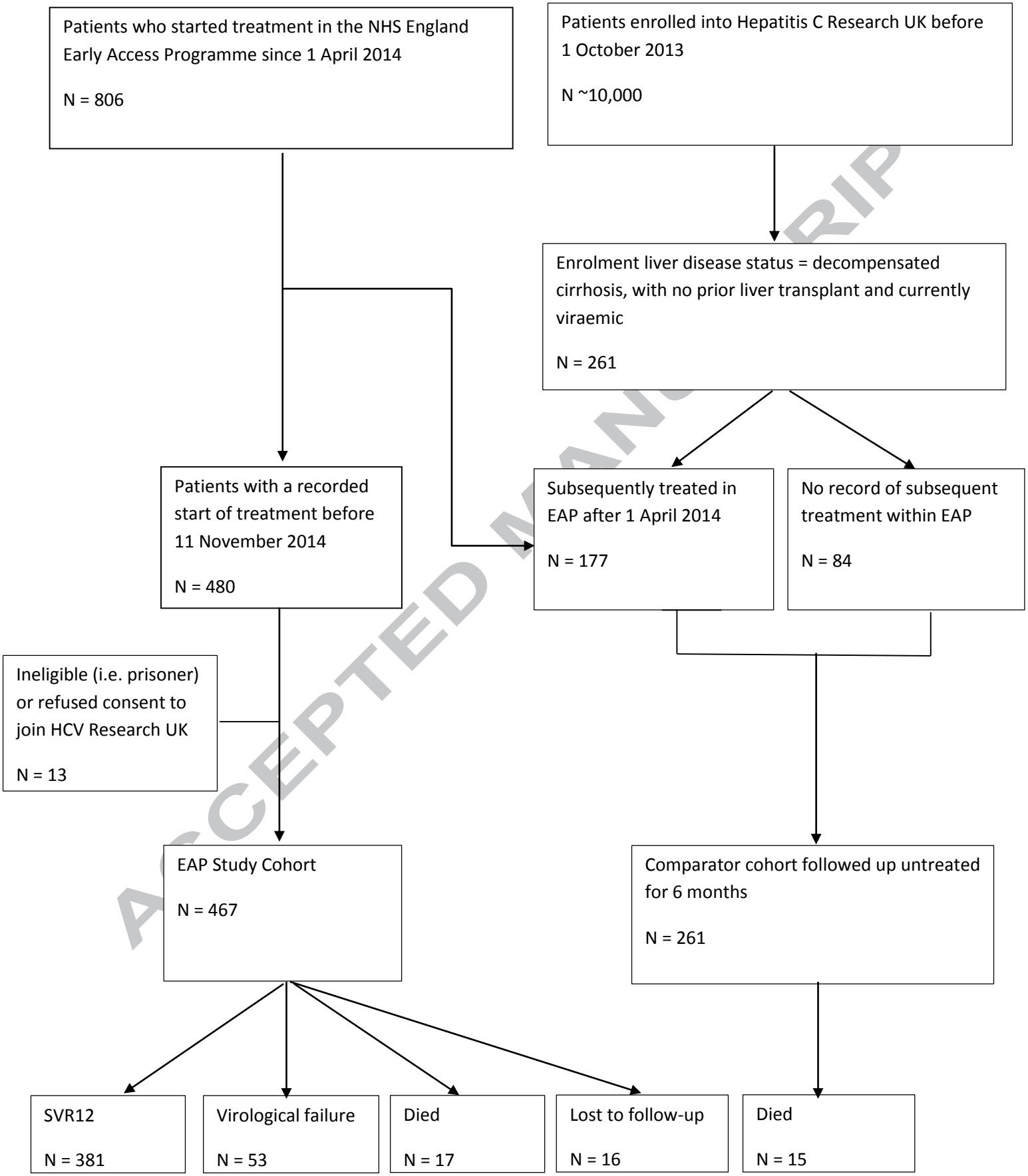
Table 1. Baseline characteristics of treated and comparator (untreated) patients.

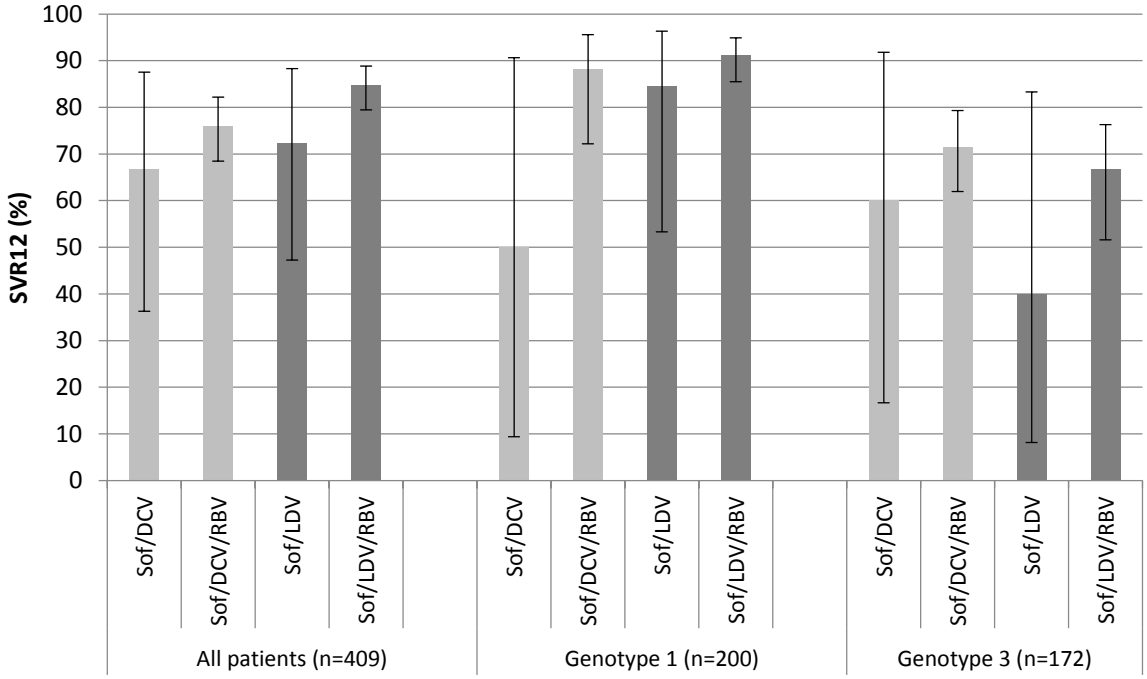
	Treatment regimen	All patients (n=467)			Decompensated patients (n=409)			OLT before baseline (n=44)			Extrahepatic patients (n=14)		
		SVR12	n	%	SVR12	n	%	SVR12	n	%	SVR12	n	%
All patients	**All**	**381**	**467**	**81.6**	**329**	**409**	**80.4**	**38**	**44**	**86.4**	**14**	**14**	**100.0**
	Sof/DCV	11	15	73.3	8	12	66.7	1	1	100.0	2	2	100.0
	Sof/DCV/RBV	133	172	77.3	114	150	76.0	14	17	82.4	5	5	100.0
	Sof/LDV	18	25	72.0	13	18	72.2	5	7	71.4	0	0	-
	Sof/LDV/RBV	219	255	85.9	194	229	84.7	18	19	94.7	7	7	100.0
Genotype 1	**All**	**209**	**231**	**90.5**	**179**	**200**	**89.5**	**25**	**26**	**96.2**	**5**	**5**	**100.0**
	Sof/DCV	3	5	60.0	2	4	50.0	1	1	100.0	0	0	-
	Sof/DCV/RBV	36	41	87.8	30	34	88.2	5	6	83.3	1	1	100.0
	Sof/LDV	16	18	88.9	11	13	84.6	5	5	100.0	0	0	-
	Sof/LDV/RBV	154	167	92.2	136	149	91.3	14	14	100.0	4	4	100.0
Genotype 3	**All**	**132**	**192**	**68.8**	**117**	**172**	**68.0**	**9**	**14**	**64.7**	**6**	**6**	**100.0**
	Sof/DCV	5	7	71.4	3	5	60.0	0	0	-	2	2	100.0
	Sof/DCV/RBV	86	118	72.9	75	105	71.4	8	10	80.0	3	3	100.0
	Sof/LDV	2	7	28.6	2	5	40.0	0	2	0.0	0	0	-
	Sof/LDV/RBV	39	60	65.0	37	57	64.9	1	2	50.0	1	1	100.0
Other	**All**	**40**	**44**	**90.9**	**33**	**37**	**89.2**	**4**	**4**	**100.0**	**3**	**3**	**100.0**
	Sof/DCV	3	3	100.0	3	3	100.0	0	0	-	0	0	-
	Sof/DCV/RBV	11	13	84.6	9	11	81.8	1	1	100.0	1	1	100.0
	Sof/LDV	-	0	-	0	0	-	0	0	-	0	0	-
	Sof/LDV/RBV	26	28	92.8	21	23	91.3	3	3	100.0	2	2	100.0

Table 2. Choice of treatment regimens according to HCV genotypes and virological response at 12 weeks post-treatment (SVR12) in patients treated on the Expanded Access Programme

			Adverse outcome (n)	Benefit (n)	Benefit	Odds ratio	95%	CI
Age / albumin (g/L) interaction terms	Age <65	Albumin ≥35	34	52	60.5	1 (Ref)		
	Age <65	Albumin <35	159	124	43.8	0.52	0.32	0.86
	Age ≥65	Albumin ≥35	6	6	50.0	0.67	0.20	2.27
	Age ≥65	Albumin <35	17	11	39.3	0.44	0.18	1.05
Baseline serum sodium (mmol/L)	≥135		135	141	51.1	1 (Ref)		
	<135		81	52	39.1	0.63	0.41	0.97

Table 3. Likelihood of functional benefit (no MELD increase and no serious adverse events) or adverse outcome (MELD increase and/or serious adverse events) following antiviral therapy based on patient baseline characteristics





All treatment durations = 12 weeks